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- (71) Applicant (for all designated States except US): GENE LOGIC, INC. [US/US]; 708 Quince Orchard Road, Gaithersburg, MD 20878 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): BEAZER-BAR-CLAY, Yasmin [US/US]; Gene Logic, Inc., 708 Quince Orchard Road, Gaithersburg, MD 20878 (US). WEISS-MAN, Sherman, M. [US/US]; Gene Logic, Inc., 708 Quince Orchard Road, Gaithersburg, MD 20878 (US). YAMAGA, Shigeru [US/US]; Gene Logic, Inc., 708 Quince Orchard Road, Gaithersburg, MD 20878 (US). VOCKLEY, Joseph [US/US]; Gene Logic, Inc., 708 Quince Orchard Road, Gaithersburg, MD 20878 (US).
- (74) Agents: CARROLL, Lawrence, J. et al.; Morgan, Lewis & Bockius LLP, 1111 Pennsylvania Avenue, NW, Washington, DC 20004 (US).
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(54) Title: GENE EXPRESSION PROFILES IN GRANULOCYTIC CELLS

(57) Abstract: The present invention identifies the global changes in gene expression associated with activation of granulocytes. The present invention also identifies expression profiles which serve as useful diagnostic markers as well as markers that can be used to monitor disease states, disease progression, drug toxicity, drug efficacy and drug metabolism.

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Table 7. Genes identified by DNA chip analysis.

Affy ID	Genbank	Seq ID	Gene Bank Names	ratio E.coli	ratio KIM5	ratio KIM6	ratio yopH
38119_at	X12496	1097	Human mRNA for erythrocyte membrane sialoglycoprotein beta (glycophorin C).	1.0	2.8	1.8	3.2
985_s_at	X12830	1098	Human mRNA for interleukin-6-receptor.	1.3	-1.6	1.2	3.3
39239_at	X13444	1099	Human mRNA for CD8 beta-chain glycoprotein (CD8 beta.1).	5.0	18.2	31.0	16.3
41231_f_at	X13546	1100	Human HMG-17 gene for non-histone chromosomal protein HMG-17.	-1.0	1.4	-1.7	-1.1
37033_s_at	X13710	1101	H.sapiens unspliced mRNA for glutathione peroxidase.	1.0	2.1	2.1	2.9
33820_g_at	X13794	1102	H.sapiens lactate dehydrogenase B gene exon 1 and 2 (EC 1.1.1.27) (and joined CDS).	-5.3	2.7	2.2	1.1
37180_at	X14034	1103	Human mRNA for phospholipase C.	-1.3	-1.1	-1.7	-1.7
31870_at	X14046	1104	Human mRNA for leukocyte antigen CD37.	1.2	-3.1	-2.8	-2.3
38610_s_at	X14487	1105	Human gene for acidic (type I) cytolysin 10.	1.0	1.0	-2.7	-1.6
40415_at	X14813	1106	Human liver mRNA for 3-oxoacyl-CoA thiolase.	-5.3	-30.8	-5.7	-3.1
33480_at	X15393	1108	H.sapiens motilin gene exon 2 (and joined CDS).	2.2	2.6	2.0	2.0
33676_at	X15940	1109	Human mRNA for ribosomal protein L31.	-1.0	-1.2	-1.4	1.4
1220_g_at	X15949	1110	Human mRNA for interferon regulatory factor-2 (IRF-2).	-4.5	1.1	-2.5	-1.4
1219_at	X15949	1110	Human mRNA for interferon regulatory factor-2 (IRF-2).	-4.5	-18.4	-16.7	-18.4
35201_at	X16135	1112	Human mRNA for novel heterogeneous nuclear RNP protein, L protein.	1.9	2.0	-1.1	-1.1
1919_at	X16316	1113	Human mRNA for vav oncogene.	-1.4	-1.1	-6.1	-1.4
988_at	X16354	1114	Human mRNA for transmembrane carcinoembryonic antigen BGPa (formerly TM1-CEA).	1.2	-2.0	1.4	-6.1
37021_at	X16832	1116	Human mRNA for cathepsin H (EC 3.4.22.16).	-4.3	1.5	-2.4	-1.5
36985_at	X17025	1117	Human homolog of yeast IPP isomerase.	1.0	-2.5	-1.6	-1.7
35338_at	X17094	1119	Human fur mRNA for furin.	-5.4	-13.2	-13.2	-13.2
31527_at	X17206	1120	Human mRNA for LLRep3.	-1.1	-2.3	-2.8	-1.7
32786_at	X51345	1121	Human jun-B mRNA for JUN-B protein.	3.4	1.7	1.4	-1.6
35251_at	X51435	1122	Human PRDII-BF1 gene for a DNA-binding protein.	-6.2	6.1	7.6	4.3
40103_at	X51521	1123	Human mRNA for ezrin.	2.8	3.2	1.5	2.0
35965_at	X51757	1124	Human heat-shock protein HSP70B' gene.	-10.9	-4.9	-4.0	-7.3
117_at	X51757	1124	Human heat-shock protein HSP70B' gene.	-10.9	-10.9	-5.4	-3.1
38515_at	X51801	1125	Human OP-1 mRNA for osteogenic protein.	1.0	4.0	1.0	7.7
788_s_at	X52001	1126	Human endothelin 3 (EDN3) mRNA, complete cds.	2.0	1.0	1.0	10.8

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What is claimed is:

1. A method of detecting granulocyte activation, comprising:
 - (a) detecting the level of expression in a sample of one or more genes from
5 Tables 2-8;
 - (b) comparing the expression level to an expression level in an un-activated granulocyte, wherein differential expression of the genes in Tables 2-8 is indicative of granulocyte activation.
- 10 2. A method of modulating granulocyte activation, comprising:
 - (a) contacting a granulocyte with an agent, wherein the agent alters the expression of at least one gene in Tables 2-8 thereby modulating granulocyte activation.
- 15 3. A method of screening for an agent capable of modulating granulocyte activation, comprising:
 - (a) preparing a first gene expression profile of a cell population comprising granulocytes, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
 - (b) exposing the cell population to the agent;
 - 20 (c) preparing second gene expression profile of the agent-exposed cell population; and
 - (d) comparing the first and second gene expression profiles.
- 25 4. A method of detecting an inflammation in a tissue, comprising:
 - (a) detecting the level of expression in a sample of the tissue of one or more genes from Tables 2-8; wherein the level of expression of the genes in Tables 2-8 is indicative of inflammation.
- 30 5. A method of treating an inflammation in a tissue, comprising:
 - (a) contacting a tissue having an inflammation with an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the inflammation.

6. A method of screening for an agent capable of modulating an inflammation in a tissue, comprising:
- (a) preparing a first gene expression profile of a sample of the tissue, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
 - (b) exposing the tissue to the agent;
 - (c) preparing second gene expression profile of the agent-exposed tissue; and
 - (d) comparing the first and second gene expression profiles.
7. A method of detecting a chronic inflammation in a tissue, comprising:
- (a) detecting the level of expression in a sample of the tissue of one or more genes from Tables 2-8; wherein the level of expression of the genes in Tables 2-8 is indicative of a chronic inflammation.
8. A method of treating a chronic inflammation in a tissue, comprising:
- (a) contacting a tissue having a chronic inflammation with an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the chronic inflammation.
9. A method of screening for an agent capable of modulating a chronic inflammation in a tissue, comprising:
- (a) preparing a first gene expression profile of a sample of the tissue, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
 - (b) exposing the tissue to the agent;
 - (c) preparing a second gene expression profile of the agent-exposed tissue; and
 - (d) comparing the first and second gene expression profiles.
10. A method of detecting an allergic response in a subject, comprising:
- (a) obtaining a sample from the subject, the sample comprising granulocytes;
 - (b) preparing a gene expression profile of the sample, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

(c) comparing the expression level to an expression level in a sample from a normal individual, wherein differential expression of the genes in Tables 2-8 is indicative of an allergic response.

- 5 11. A method of treating an allergic response in a subject, comprising:
- (a) administering to the subject an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the allergic response.
- 10 12. A method of screening for an agent capable of modulating an allergic response in a subject, comprising:
- (a) preparing a first gene expression profile of a sample from the subject, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
- 15 (b) administering to the subject an agent;
- (c) preparing a second gene expression profile of a sample from the agent-exposed subject; and
- (d) comparing the first and second gene expression profiles.
- 20 13. A method of detecting exposure of a subject to a pathogen, comprising:
- (a) preparing a first gene expression profile of a granulocyte population from the subject, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
- (b) comparing the first gene expression profile to a second gene expression
- 25 profile from a granulocyte population exposed to the pathogen and to a third gene expression profile from a granulocyte population not exposed to the pathogen; and
- (c) determining whether the subject was exposed to the pathogen.
14. A method of treating a subject exposed to a pathogen, comprising:
- 30 (a) administering to the subject an agent, wherein the agent affects the expression of at least one gene in Tables 2-8 thereby treating the subject.

15. A method of screening for an agent that modulates a response of a granulocyte population to a pathogen, comprising:

(a) preparing a first gene expression profile of a first sample from the granulocyte population, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

(b) exposing a second sample of the granulocyte population to a pathogen and preparing a second gene expression profile from the second sample;

(c) contacting the pathogen-exposed granulocyte population with an agent and preparing a third gene expression profile from the agent-contacted pathogen-exposed population;

(d) comparing the first, second and third gene expression profiles; and

(e) identifying agents that modulate the response of a granulocyte population to the pathogen.

16. A method of detecting a sterile inflammatory disease in a subject, comprising:

(a) detecting the level of expression in a sample from the subject of one or more genes from Tables 2-8; wherein the level of expression of the genes in Tables 2-8 is indicative of a sterile inflammatory disease.

20

17. A method of treating a sterile inflammatory disease in a subject, comprising:

(a) contacting the subject with an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the sterile inflammatory disease.

25

18. A method of screening for an agent capable of modulating a sterile inflammatory disease in a subject, comprising:

(a) preparing a first gene expression profile of a sample from the subject, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

30

(b) exposing the subject to the agent;

(c) preparing second gene expression profile of a sample obtained from the

agent-exposed subject; and

(d) comparing the first and second gene expression profiles.

19. A composition comprising at least two oligonucleotides, wherein each of
5 the oligonucleotides comprises a sequence that specifically hybridizes to a gene in Tables
2-8.

20. A composition according to claim 19, wherein the composition comprises
at least 3 oligonucleotides, wherein each of the oligonucleotides comprises a sequence that
10 specifically hybridizes to a gene in Tables 2-8.

21. A composition according to claim 19, wherein the composition comprises
at least 5 oligonucleotides, wherein each of the oligonucleotides comprises a sequence that
specifically hybridizes to a gene in Tables 2-8.

22. A composition according to claim 19, wherein the composition comprises
at least 7 oligonucleotides, wherein each of the oligonucleotides comprises a sequence that
specifically hybridizes to a gene in Tables 2-8.

23. A composition according to claim 19, wherein the composition comprises
at least 10 oligonucleotides, wherein each of the oligonucleotides comprises a sequence
that specifically hybridizes to a gene in Tables 2-8.

24. A composition according to any one of claims 19-23, wherein at least one
25 oligonucleotide is attached to a solid support.

25. A composition according to claim 24, wherein the solid support is selected
from a group consisting of a membrane, a glass support, a filter, a tissue culture dish, a
polymeric material, a bead and a silica support.

26. A solid support comprising at least two oligonucleotides, wherein each of
the oligonucleotides comprises a sequence that specifically hybridizes to a gene in Tables
2-8.

27. A solid support according to claim 26, wherein at least one of the oligonucleotides is covalently attached to the solid support.
- 5 28. A solid support according to claim 26, wherein at least one of the oligonucleotides is non-covalently attached to the solid support.
29. A solid support according to claim 26, wherein the support comprises at least 10 different oligonucleotides in discrete locations per square centimeter.
- 10 30. A solid support according to claim 26, wherein the support comprises at least 100 different oligonucleotides in discrete locations per square centimeter.
31. A solid support according to claim 26, wherein the support comprises at least 1000 different oligonucleotides in discrete locations per square centimeter.
- 15 32. A solid support according to claim 26, wherein the support comprises at least 10,000 different oligonucleotides in discrete locations per square centimeter.
- 20 33. A computer system comprising:
(a) a database containing information identifying an expression level in a cell population comprising granulocytes of a set of genes comprising at least two genes in Tables 2-8; and
(b) a user interface to view the information.
- 25 34. A computer system of claim 33, wherein the database further comprises sequence information for the genes.
- 30 35. A computer system of claim 33, wherein the database further comprises information identifying the expression level for the set of genes in a cell population comprising non-activated granulocytes.

36. A computer system of claim 33, wherein the database further comprises information identifying the expression level of the set of genes in a cell population comprising activated granulocytes.

5 37. A computer system of any of claims 33-36, further comprising records including descriptive information from an external database, which information correlates said genes to records in the external database.

10 38. A computer system of claim 37, wherein the external database is GenBank.

39. A method of using a computer system of any one of claims 33-36 to present information identifying the expression level in a tissue or cell of at least one gene in Tables 2-8, comprising:

15 (a) comparing the expression level of at least one gene in Tables 2-8 in the tissue or cell to the level of expression of the gene in the database.

40. A method of claim 39, wherein the expression level of at least two genes are compared.

20 41. A method of claim 39, wherein the expression level of at least five genes are compared.

25 42. A method of claim 39, wherein the expression level of at least ten genes are compared.

43. A method of claim 39, further comprising displaying the level of expression of at least one gene in the tissue or cell sample compared to the expression level in a cell population comprising activated granulocytes.

30 44. A method of identifying virulence factor genes in a pathogen, comprising:
(a) preparing a first gene expression profile of a quiescent granulocyte population;
(b) preparing a second gene expression profile of a granulocyte population

exposed to a virulent or avirulent strain of pathogen;

(c) preparing a third gene expression profile from a granulocyte population exposed to a strain of pathogen with a mutation in a putative virulence factor gene; and

(d) comparing the first, second and third gene expression profiles to identify
5 a virulence factor gene of the pathogen.

ID ABK84542 standard; cDNA; 2757 BP.
 XX
 AC ABK84542;
 XX
 DT 14-AUG-2002 (first entry)
 XX
 DE Human cDNA differentially expressed in granulocytic cells #1113.
 XX
 KW Human; ss; granulocytic cell; DNA chip; bacterial infection;
 KW viral infection; parasitic infection; protozoal infection;
 KW fungal infection; sterile inflammatory disease; psoriasis;
 KW rheumatoid arthritis; glomerulonephritis; asthma; thrombosis;
 KW cardiac reperfusion injury; renal reperfusion injury; ARDS;
 KW adult respiratory distress syndrome; inflammatory bowel disease;
 KW Crohn's disease; ulcerative colitis; periodontal disease;
 KW granulocyte activation; chronic inflammation; allergy.
 XX
 OS Homo sapiens.
 XX
 PN WO200228999-A2.
 XX
 PD 11-APR-2002.
 XX
 PF 03-OCT-2001; 2001WO-US30821.
 XX
 PR 03-OCT-2000; 2000US-237189P.
 XX
 PA (GENE-) GENE LOGIC INC.
 XX
 PI Beazer-Barclay Y, Weissman SM, Yamaga S, Vockley J;
 XX
 DR WPI; 2002-435328/46.
 XX
 PT Detecting granulocyte activation by detecting differential expression
 PT of genes associated with granulocyte activation, which serves as
 PT diagnostic markers that is useful for monitoring disease states and
 PT drug toxicity -
 XX
 PS Claim 1; SEQ ID No 1113; 114pp; English.
 XX
 CC The invention relates to detecting (M1) granulocyte (GC) activation
 CC (GCA), by detecting the level of expression of gene(s) (Gs) identified by
 CC DNA chip analysis as given in the specification, and comparing
 CC the expression level to an expression level in an unactivated
 CC GC, where differential expression of Gs is indicative of GCA.
 CC Also included are modulating (M2) GA by contacting GC with an agent
 CC that alters the expression of at least one gene in Gs; (2) screening (M3)
 CC for an agent capable of modulating GCA or an inflammation (especially
 CC chronic) in a tissue, an allergic response in a subject, exposure of a
 CC subject to a pathogen or sterile inflammatory disease using the
 CC gene expression profile; (3) detecting (M4) an inflammation (especially
 CC chronic) in a tissue, an allergic response in a subject, exposure of a
 CC subject to a pathogen or sterile inflammatory disease, by detecting the
 CC level of expression in a sample of the tissue of gene(s) from Gs, where
 CC the level of expression of the gene is indicative of inflammation;
 CC (4) treating (M5) an inflammation (especially chronic) or in a tissue,
 CC an allergic response in a subject, exposure of a subject to a pathogen
 CC or sterile inflammatory disease, by contacting a tissue having
 CC inflammation with an agent that modulates the expression of gene(s)
 CC from Gs in the tissue. M1 is useful for detecting GCA; M2 is useful for
 CC modulating GA; M3 is useful for screening an agent capable of modulating
 CC GCA preferably in an inflammation in a tissue; M4 is useful for
 CC detecting an inflammation (especially chronic) in a tissue, an allergic
 CC response in a subject, exposure of a subject to a pathogen or sterile

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CC inflammatory disease (e.g. psoriasis, rheumatoid arthritis,
 CC glomerulonephritis, asthma, thrombosis, cardiac reperfusion injury, renal
 CC reperfusion injury, ARDS, adult respiratory distress syndrome,
 CC inflammatory bowel disease, Crohn's disease, ulcerative colitis,
 CC periodontal disease; also bacterial infection, viral infection,
 CC parasitic infection, protozoal infection, fungal infection and M5 is
 CC useful for treating one of the above conditions. The present
 CC sequence represents a gene differentially expressed in granulocytes.
 CC Note: The sequence data for this patent did not form part
 CC of the printed specification, but was obtained in electronic
 CC format directly from WIPO at
 CC ftp.wipo.int/pub/published_pct_sequences.

XX
 SQ

Sequence 2757 BP; 693 A; 713 C; 809 G; 542 T; 0 other;

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